Technical Considerations: Defining Manufacturing Standards, Regulatory Needs, and Capacity and Role of Clinical Trials

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Types of licensed monovalent pandemic influenza A (H1N1) 2009 vaccines


Whole virus


Split virus


Subunit
(surface antigen)

(Source: IFPMA-IVS)


Live attenuated

Baxter cell culture (EMEA) **Ommnivest (Hungary)**	**8 manufacturers, (China)** **4 manufacturers (Japan)** **CSL (Australia; US)** **Sanofi Pasteur (US)** **Green Cross (Korea)** **GSK ASO3 (EMEA, Canada)**	**Novartis (US)** **Novartis+M59 adjuvant (EMEA)** **Novartis cell culture (Germany)**	**MedImmune (US)** **Microgen (Russia)**

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Defining manufacturing standards

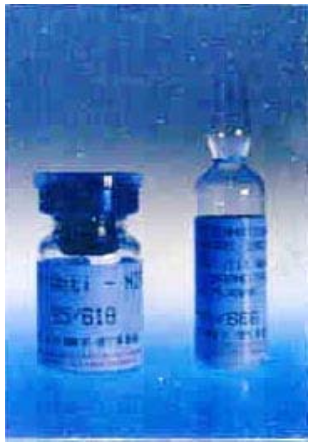
- Influenza vaccines are mature products and manufacturing standards are well standardized
- International mechanisms exist, via WHO, to achieve standardization at the international level
- Example – potency of inactivated influenza vaccines is expressed in ug of HA around the world
- Problems – supplying sufficient reagents in sufficient time is often a challenge

International biological standardization

Global written standards

www.who.int/biologicals

Global measurement standards



More than 250 WHO measurement Standards are available; define the IU

Global consensus

1) Standardization of assays
2) Development and refinement of QC tests
3) Scientific basis for setting specifications

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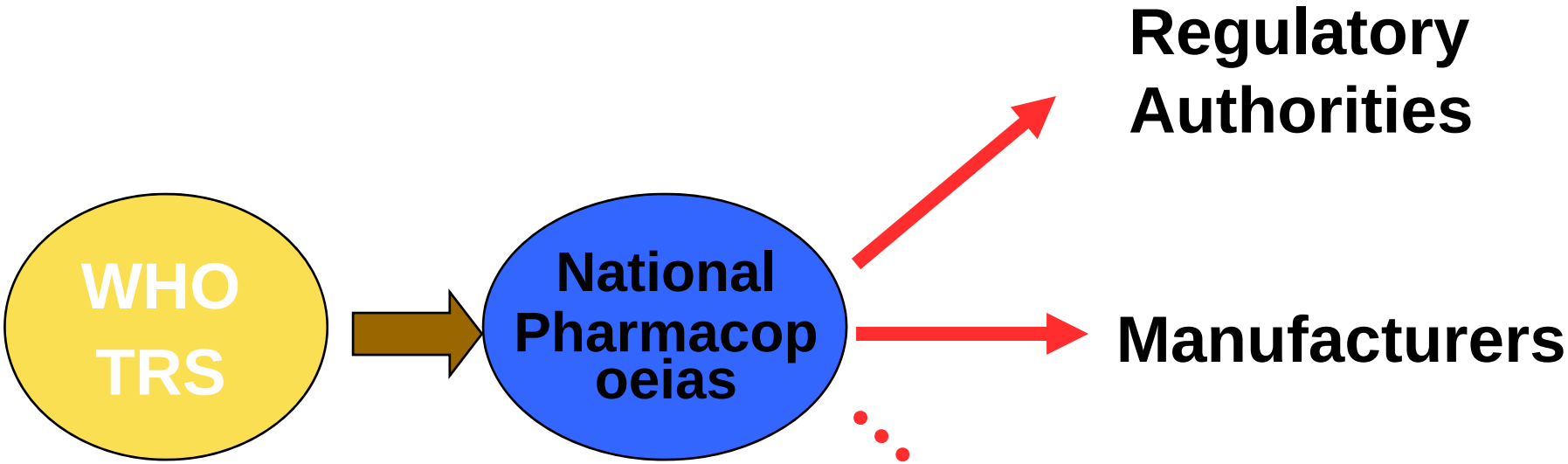
WHO Written Standards

A tool for harmonization of specifications worldwide



Technical specifications defined in TRS are the standard used for prequalification purposes

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Regulatory approval needs

- Categories of information needed to obtain regulatory approval of influenza vaccines are similar in all countries – data on the quality, safety and efficacy of the product; international expectations defined in WHO standards
- In general, regulatory data requirements vary with the level of pre-existing knowledge of the new vaccine
- Vaccines which are a strain change to an already licensed product, can licensed on the basis of laboratory tests only; clinical data have been required, if at all, as a post-licensure commitment
- Candidate vaccines produced using novel technologies, or produced by new manufacturers, require a full regulatory package and correspondingly lengthier time to licensure

Regulatory collaborations

- Preparations, facilitated by WHO, over several years have resulted in a high degree of regulatory preparedness for pandemic influenza vaccines
- A high degree of regulatory collaboration has been established between influenza regulators through a WHO-led regulators forum to manage emerging regulatory issues during the pandemic
- Potentially important resource to support regulators in the future in additional countries that are new to influenza vaccine production

Role of clinical trials

- Clinical trials are needed for new vaccines (new products, new manufactures) since we are still learning new things about influenza (eg that the H1N1 pandemic vaccine was highly immunogenic after 1 dose)
- Standards are required to enable better comparison of clinical trial data - eg 1st International Standard for influenza antibody against clade 1 H5 virus
- Better understanding of immune correlates of immunity are needed too

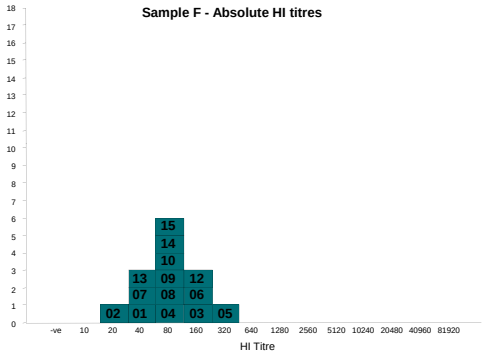
Between laboratory variability for H5 clade 1 virus – use of WHO standard 07/150

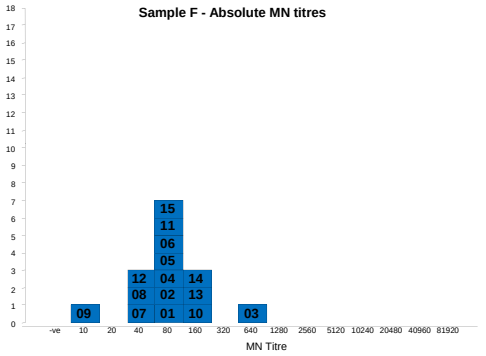
Test serum F – EU post vaccination serum

HI assay

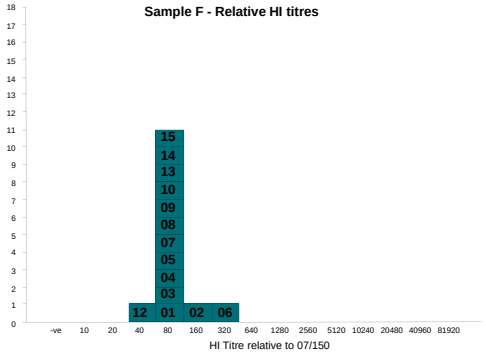
MN assay

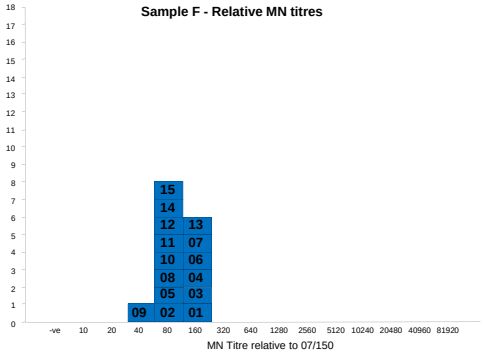
A/Vietnam/2004 titres





A/Vietnam/2004 titres relative to 07/150





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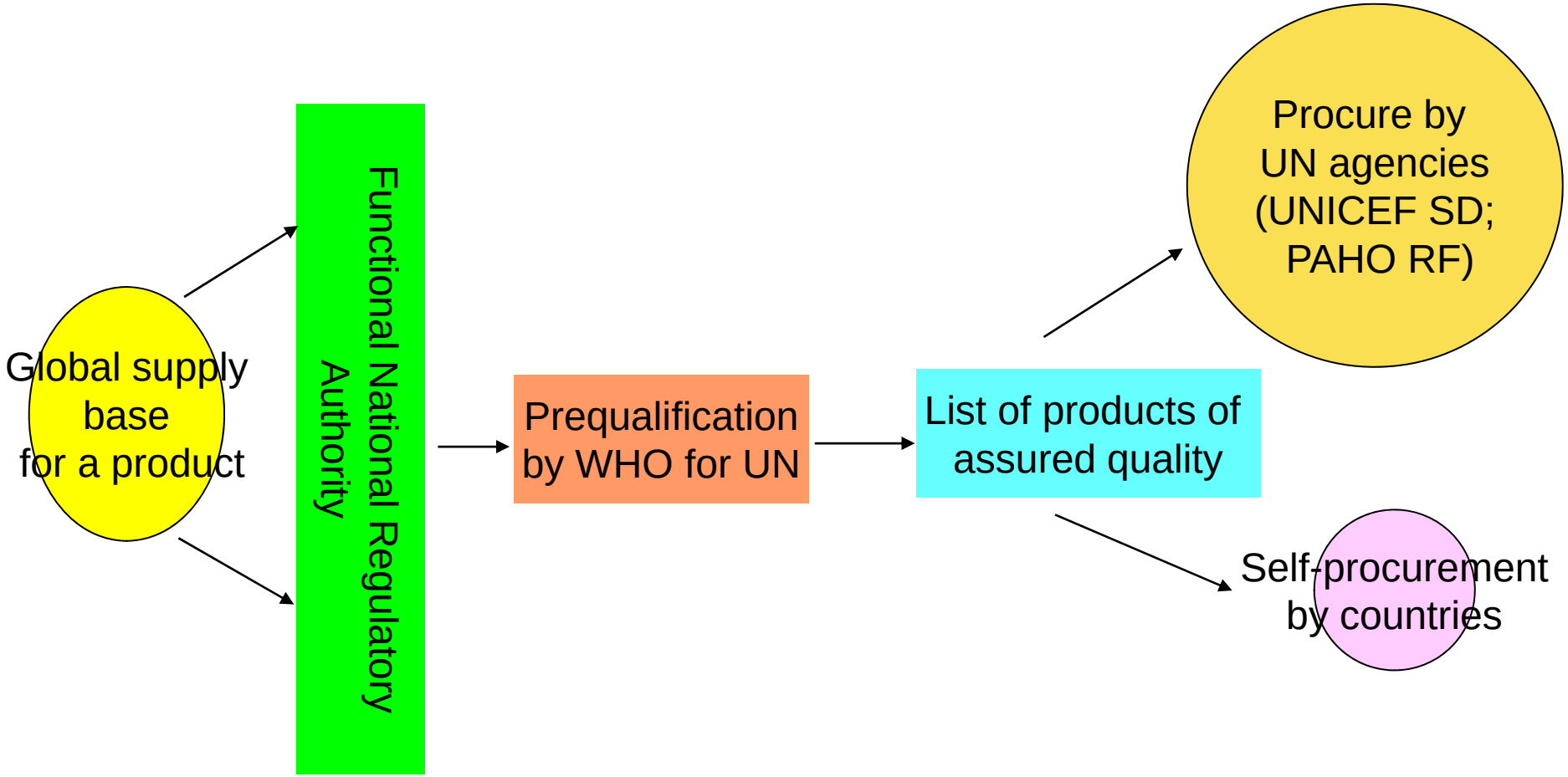
WHO prequalification – facilitating sustainable production of vaccines of assured quality



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Vaccines prequalified by WHO: status 2009 (assured quality)

12 *industrialized country mfrs*

- ✓ Belgium
- ✓ Denmark
- ✓ France
- ✓ Germany
- ✓ The Netherlands
- ✓ Hungary
- ✓ Italy
- ✓ Japan
- ✓ Rep. of Korea
- ✓ USA
- ✓ Switzerland
- ✓ Sweden

6 *emerging economy country mfrs*

- ✓ Brazil
- ✓ Bulgaria
- ✓ Cuba
- ✓ India
- ✓ Indonesia
- ✓ Russia
- ✓ Senegal

26 manufacturers

104 pre-qualified vaccines

used in **112** countries

53% total population

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Conclusions

- Influenza vaccines are mature products and manufacturing standards are well standardized, up to and including the international level
- Regulatory needs are similar, from scientific perspective, for all countries
- Global regulatory collaboration is achievable, eg WHO-led regulatory forum for the pandemic, and could be a support mechanism for new regulators in countries new to influenza vaccine production
- Clinical trials are needed for new vaccines (new products, new manufacturers) since we are still learning new things about influenza (eg immunogenicity of 1 dose of H1N1 pandemic vaccine)
- The WHO prequalification scheme provides the a mechanism for influenza vaccines of assured quality to access international markets